

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

SAF312

CSAF312X2201

A randomized, vehicle-controlled, subject and investigator-masked, proof-of-concept study to evaluate the use of topical ocular SAF312 in the treatment of postoperative ocular pain in patients undergoing photorefractive keratectomy (PRK) surgery

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial “**CSAF312X2201**”.

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Final study protocol (V02) is available at the time of finalization of Statistical Analysis Plan.

1.3 Study objectives

1.3.1. Primary objective(s)

<i>Primary objective(s)</i>	<i>Endpoints related to primary objectives</i>
<ul style="list-style-type: none">To evaluate pain control in the immediate post-operative period.	<ul style="list-style-type: none">Visual analog scale (VAS) pre-dose pain assessment at 6 hours post-operatively.Average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour assessment.

1.3.2. Secondary objective(s)

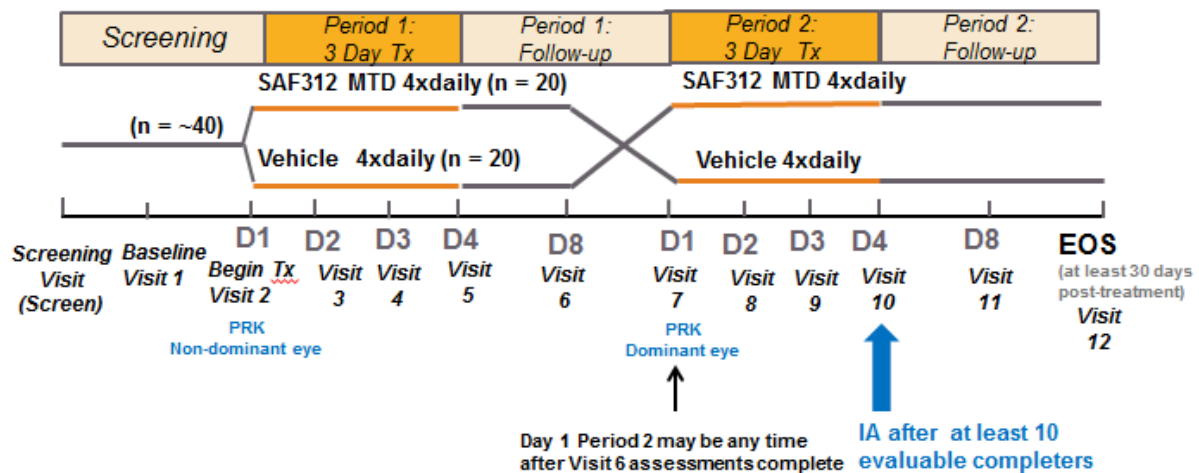
<i>Secondary objective(s)</i>	<i>Endpoints related to secondary objective(s)</i>
<ul style="list-style-type: none">To evaluate the efficacy of SAF312 eye drops four times daily for reducing use of oral analgesics following PRK procedure.	<ul style="list-style-type: none">Incidence of and amount of rescue oral analgesics needed in 6 hours, 12 hours, 24 hours, 2 days, and 3 days post-operatively after each PRK surgery.
<ul style="list-style-type: none">To assess the safety and tolerability of SAF312 eye drops four times daily.	<ul style="list-style-type: none">AEs and SAEs.Visual acuity, intraocular pressure (IOP), dilated fundus exam, ocular hyperemia.Size of epithelial defect by slit lamp exam.Blink rate, tear productionVital signs (blood pressure, pulse rate, and body temperature).

<ul style="list-style-type: none">• To evaluate pain severity post-operatively	<ul style="list-style-type: none">• All VAS measurements during the first 3 days after surgery.
<ul style="list-style-type: none">• To assess the systemic exposure after ocular dosing of SAF312 eye drops four times daily at various time points in PRK patients.	<ul style="list-style-type: none">• Plasma concentration of SAF312.

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1.4 Study design and treatment

This is a proof-of-concept, subject and investigator-masked, randomized, vehicle controlled study of SAF312 administered as eye drops in addition to standard of care treatments in patients after photorefractive keratectomy (PRK) surgery. Patients will be randomized to two sequences: 1) SAF312, followed by vehicle, or 2) vehicle, followed by SAF312. Each patient will receive the assigned dose four times daily for 72 hours following PRK surgery on their study eye (Day 1, Periods 1 and 2). The initial study eye will be the non-dominant eye as established at screening and in agreement of the patient and the PI. Each patient will return for follow-up visits on Days 2, 3, 4 and 8 after surgery of Periods 1 and 2.

Figure 1-1: Study design

2 First interpretable results (FIR)

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The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be highlighted in TFL shells document and marked as “Key” in the Programming Deliverables Tracker (PDT) output list.

FIR will focus on the following analyses:

- Analysis populations (if needed)
- Subject disposition
- Demographics and baseline characteristics.
- Safety results
 - Number and percentage of subjects with adverse events by body system – Ocular
 - Number and percentage of subjects with adverse events by body system – Non-ocular
 - Overall incidence of AEs—number of events and number of subjects, to include AEs of mild, moderate and severe intensity, SAEs, AEs leading to discontinuation of study and Study-drug related AEs leading to discontinuation of study.
- Pharmacokinetic results for plasma:
 - Total SAF312 plasma concentration-time profiles: Overlaying mean (SD) plot.
- Pharmacodynamic analyses will be provided for the completers population
Pharmacodynamic analyses will include, but are not limited to:

- Table of model estimated treatment comparison of VAS pain assessment at 6 hours post-operatively
- Plot of model estimated means with SE of VAS pain assessment over time by treatment (overlaid).
- Table of model estimated treatment comparison of average VAS pain assessment (0-12hr)
- Proportion of oral analgesics use incidence
- McNemar's test of oral analgesics use incidence
- Summary of the amount of oral analgesics use by treatment during the four time intervals
- Wilcoxon signed rank test of the amount of oral analgesics tablets during the four time intervals: 0-6 hours post-operatively, 0-12 hours post-operatively, 0-24 hours post-operatively, 0-2 days post-operatively and 0-3 days post-operatively
- Histogram of patients taking 0, 1, 2, 3, or 4 rescue oral analgesic tablets during the first 24 hours after surgery (0-24 hours post-operatively) by treatment.

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4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment, the treatment actually received will be used for the analysis.

For subjects for which the actual sequence of treatments received does not match the randomized sequence of treatments, the actual sequence will be used for analysis involving a sequence component (e.g. ANOVAs with a sequence effect) if the actual sequence is one of the sequences planned in the study design. If the actual sequence is not one of the sequences planned in the study design, the actual randomized sequence will be used for analysis involving a sequence component but data points from periods in which the subject has not received the randomized treatment will be excluded from the analysis.

All subjects that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The primary PD analysis set for primary efficacy analysis will contain all patients who experienced no protocol deviations with relevant impact on VAS data.

The secondary PD analysis set will contain all patients who experienced no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all (<i>safety</i>) analysis in case of these PDs:		Exclude subject completely from all (<i>safety</i>) analysis sets
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis set
Subjects are excluded from primary PD analysis in case of these PDs:		Exclude subject from primary PD analysis set
OTH13	VAS data entry mechanism issue affecting all visits	

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from secondary PD analysis in case of these PDs:		Exclude subject from secondary PD analysis sets

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

5.1 Variables

The following pharmacokinetic parameters will be determined as feasible, assuming sufficient data exists, using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): C_{max}, C_{min} (pre-dose), T_{max}, AUC_{last}, AUC_{0-t}, C_{last} and T_{last} from the plasma concentration-time data. Other PK parameters may be calculated if deemed necessary.

5.2 Descriptive analyses

SAF312 plasma concentrations will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point including the frequency and percentage of concentrations below LLOQ.

Pharmacokinetic parameters will be calculated as described in Section 5.1 and will be listed by treatment and subject. Descriptive summary statistics will be provided by treatment and visit.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum, and the frequency (n, %) of concentrations below the LLOQ. An exception to this is T_{max} where only median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Graphical methods will be employed to show mean and individual concentration-time profiles:

- Arithmetic mean (SD) of SAF312 plasma concentration data will be plotted across time in both linear view and semi-logarithm view.
- Overlaying individual SAF312 plasma concentration-time profiles by day as applicable will be generated.
- Individual SAF312 plasma concentration-time profiles will be generated.

Graphical methods will be employed to show mean C_{min} time profiles.

6 Statistical methods for Pharmacodynamic (PD) parameters

The primary and secondary analyses will be performed on the PD dataset.

6.1 Primary objective

The primary objective of this trial is to evaluate pain control in the immediate post-operative period.

6.1.1 Variables

The primary variables are visual analog scale (VAS) pre-dose pain assessment at 6 hours post-operatively, and the average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment.

6.1.2 Descriptive analyses

The VAS individual assessments will be listed by treatment sequence, subject and visit/time. Descriptive statistics will be provided by treatment and visit/time. Summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum. Graphical methods will be employed to show arithmetic mean plots with SD over time by treatment.

The average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment will also be listed by treatment sequence and subject. Descriptive statistics will be provided by treatment. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, maximum. Boxplots will be employed to visualize the data by treatment.

6.1.3 Statistical model, assumptions and hypotheses

VAS pain assessment at 6 hours post-operatively

A longitudinal mixed effect model accounting for the cross-over effect with repeated measurement for VAS will be used, with all assessments post-operatively for each period included in the analysis up to 3 days post-operatively. The model will include fixed effects of treatment, hour post-operatively, period, sequence, the treatment-by-hour post-operatively interaction, the hour post-operatively-by-period interaction, and the hour post-operatively-by-sequence interaction. Repeated measurement over hour post-operatively-by-period for each subject will be accounted for using random effects for subjects, for subject-treatment combinations within a sequence, and for subject-timepoint combinations within a sequence. Kenward-Roger method will be used for approximating the denominator degrees of freedom. Should model convergence issues occur, the team will choose an appropriate statistical model which converges adequately for treatment effect estimation. Least square means will be estimated for each treatment-by-hour post-operatively combination for each treatment and the corresponding 90% confidence intervals will be obtained. The difference between SAF312 and vehicle, the two-sided p-value, and the corresponding 90% confidence interval will be obtained from the model at each time point. The outcome of interest will be the comparison of SAF312 versus vehicle at the assessment occurring prior to the 6-hour dose post-operatively.

VAS pain assessment average up to 12 hours post-operatively

The analysis will assess the average ocular pain VAS assessments from the first post-operative assessment up to the pre-dose 12 hour post-operative assessment compared to vehicle.

A mixed effect model accounting for the cross-over effect for natural logarithmic transformed average (0-12hr) will be used. The model will include fixed effects of treatment, period, and sequence and a random effect of subject. Should model convergence issues occur, the team will choose an appropriate statistical model which converges adequately for treatment effect estimation. Kenward-Roger method will be used for approximating the denominator degrees of freedom. Least square geometric means will be estimated for each treatment and the corresponding 90% confidence intervals will be obtained by back transforming the estimates to the original scale. The geometric mean ratio between SAF312 and vehicle, the two-sided p-value, and the corresponding 90% confidence interval will be obtained from the model.

6.1.3.1 Handling of missing values/censoring/discontinuations

An additional equal number of subjects may be enrolled for subjects who withdraw from the study for reasons other than safety. Decisions regarding enrollment of these additional subjects will be discussed with the sponsor on a case-by-case basis.

6.1.3.2 Graphical presentation of results

Model estimated means of the VAS assessments with SE over time by treatment (overlaid) will be used to present the model results.

6.1.3.3 Sensitivity analyses

To account for the potential influence of the rescue medication on the primary endpoints, three different approaches of analyzing the VAS pain scores and calculating the average (0-12hr) (assuming that the influence window of rescue medication is 4 hours) will be used:

1. any recorded VAS pain score at time points within 4 hours after the use of rescue oral analgesics will be considered missing;
2. all the recorded VAS pain scores will be used;
3. any recorded VAS pain score at time points within 4 hours after the use of rescue medication will be imputed by the record taken prior to the use of rescue medication.

All three approaches will be used as sensitivity for help with the decision making.

An analysis on the log odds of VAS may be added to address the concern that the vehicle population may present differently from the literature, which could affect the hypothesized effect size.

6.2 Secondary objective

The secondary objective is to evaluate the efficacy of SAF312 eye drops four times daily for reducing use of oral analgesics following PRK procedure.

6.2.1 Variables

The secondary variables are:

1. Incidence of rescue oral analgesics: Number of patients who do not use oral analgesics in the four time intervals: 0-6 hours post-operatively, 0-12 hours post-operatively, 0-24 hours post-operatively, 0-2 days post-operatively and 0-3 days post-operatively.
2. Amount (mg/kg of body weight) of rescue oral analgesics needed during the four time intervals: 0-6 hours post-operatively, 0-12 hours post-operatively, 0-24 hours post-operatively, 0-2 days post-operatively and 0-3 days post-operatively.
3. Amount (number of pills) of rescue oral analgesics needed during the four time intervals: 0-6 hours post-operatively, 0-12 hours post-operatively, 0-24 hours post-operatively, 0-2 days post-operatively and 0-3 days post-operatively.

6.2.2 Descriptive analyses

The variables will be listed by treatment sequence, subject and visit/time interval and descriptive statistics will be provided by treatment and visit/time interval. For continuous variables summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum. Categorical variables will be summarized in frequency tables by treatment and visit/time.

Graphical methods will be employed to show group summary plots by time interval and by treatment as required. Histograms of patients taking 0, 1, 2, 3, or 4 rescue oral analgesic tablets during the first 24 hours after surgery (0-24 hours post-operatively) will be provided by treatment.

6.2.3 Statistical model, assumptions and hypotheses

Incidence of rescue oral analgesics

The McNemar's test will be used to analyze the difference of the numbers of patients who take or do not take oral analgesics between SAF312 and vehicle during the five time intervals of interest. The associated p-values will be reported.

Amount of oral analgesics needed

The amount (mg/kg body weight, and number of pills) of oral analgesics needed during the five time intervals of interest will be analyzed by Wilcoxon signed rank test. The associated p-values will be reported.

6.2.3.1 Supportive analyses

The amount (mg/kg body weight, and number of pills) of oral analgesics during each of the five time intervals will be analyzed using a generalized linear mixed effect model. The distribution of the amount will be assumed to be Beta-Binomial. The model will include fixed effects of treatment, period, and sequence and a random effect of subject. The estimated mean and the difference of the two groups, with the associated p-values and the 90% confidence intervals will be reported.

7 Statistical methods for safety and tolerability data

All subjects within the Safety analysis set will be included in the safety data analysis.

7.1.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), and ocular assessments (Visual acuity, Intraocular pressure, Dilated fundus exam, Ocular hyperemia, Size of epithelial defect by slit lamp exam, blink rate, tear production), as well as subject demographics, baseline characteristics, and treatment information.

7.1.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment sequence and subject.

Vital signs

All vital signs data will be listed by treatment sequence, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject. Ocular and non-ocular adverse events will be listed and summarized separately.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment within the following time windows: overall, acute (AE's occurring within 8 days post-operatively in each period and extended period (AE's occurring beyond 8 days post-operatively in each period if applicable). An adverse event starting in one period and continuing into the next period is counted only in the onset period. A subject with multiple adverse events within a body system and treatment period is only counted once towards the total of this body system and treatment.

Ocular assessments

All ocular assessments will be listed by subject and visit/time. Summary statistics will be provided descriptively by treatment, visit/time and eye.

7.1.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals) will be created.

Mean and boxplot figures will be presented for selected ocular parameters as needed.

